Cardiovascular involvement in patients with systemic sclerosis: insights from electromechanical characteristics of the heart

Sistemik sklerozlu hastalarda kardiyovasküler tutulum: Kalbin elektromekanik özelliklerinden çıkarsamalar

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ABSTRACT

Systemic sclerosis is a severe, life threatening autoimmune disease involving the skin and visceral organs, including the lungs, gastrointestinal tract, kidneys and heart. Cardiac involvement in systemic sclerosis, which is an important mortality predictor may involve myocardium, conduction system, vascular wall, pericardium, pulmonary vessels causing pulmonary hypertension. Thus, the detection of cardiac involvement is necessary in systemic sclerosis. With the more widespread use of novel non-invasive imaging techniques, the cardiac involvement is more frequently encountered in daily practice. Noninvasive evaluation can offer an advantage in early prediction of poor prognosis and give a chance to apply new therapeutic approaches for cardiac involvement. In this review, we intend to present cardiac involvement of systemic sclerosis and clinical diagnostic modalities, including electromechanical properties of the atrium and ventricles, for assessment this involvement. *(Anadolu Kardiyol Derg 2011; 11: 643-7)*

Key words: Cardiac involvement of systemic sclerosis, electromechanical properties of the heart, Doppler echocardiography, cardiac magnetic resonance

ÖZET

Sistemik skleroz; kalp, böbrek, mide-bağırsak sistemi, akciğer gibi iç organları ve deriyi tutan önemli ve hayatı tehdit edici otoimmün bir hastalıktır. Pulmoner hipertansiyona yol açan pulmoner damar tutulumu, perikart, damar duvarı, ileti sistemi ve miyokart tutulumu şeklinde olan kalp tutulumunun varlığı önemli bir ölüm belirtecidir. Bu nedenle, sistemik sklerozlu hastalarda kalp tutulumunu tespit etmek gerekmektedir. Bu tutulumu, girişimsel yöntemler yerine girişimsel olmayan yöntemlerle saptayabilmek amacıyla yapılan çalışmalar yeni görüntüleme yöntemleri ışığında gün geçtikçe artmaktadır. Girişimsel olmayan değerlendirmeler; olası kötü sonlanım noktalarının erken öngörülmesinde avantajlı olabilir ve sistemik sklerozlu hastalardaki kardiyak tutulumu hedef alan yeni tedavi yaklaşımlardan yararlanma fırsatı yaratabilir. Bu derlemede, sistemik sklerozun kalp tutulumunu ve bu tutulumu göstermek amacıyla kullanılan atriyum ve ventrikül elektromekanik özellikler de dahil olmak üzere, tanısal yöntemleri sunmak istedik. *(Anadolu Kardiyol Derg 2011; 11: 643-7)*

Anahtar kelimeler: Sistemik skleroz'da kalp tutulumu, kalbin elektromekanik özellikleri, Doppler ekokardiyografi, kardiyak manyetik rezonans

Introduction

Systemic sclerosis (SSc) is a severe, life threatening autoimmune disease involving the skin and visceral organs, including the lungs, gastrointestinal tract, kidneys and heart, with an annual incidence of 0.6-19.0 cases per million people (1). The disease occurs predominantly in women and onset between 30 and 55 years. SSc is characterized by tissue fibrosis due to accumulation of collagen and other extracellular matrix proteins. Its cause is unknown, but its pathophysiology involves microvascular disorders, ischemia, and fibroblast over-reactivity (2, 3). The diagnosis was defined with one major criterion being tightness, non-pitting, thickening and changes proximal to the metacarpophalangeal or metatarsophalangeal joints (4). The presence of two or more of these features contributed further as minor criteria, which are sclerodactyly limited to the

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fingers, digital pitting scars of fingertips or loss of substance of the distal finger pad and bibasilar pulmonary fibrosis.

SSc has two main clinical subset; which are limited and diffuse cutaneous forms. **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactylia, **T**eleangiectasia (CREST) syndrome is a variant of limited SSc. CREST progression is slow and involvement of internal organs is limited (5). Diffuse cutaneous SSc is progressive and 5 years mortality was shown to be 40-50%. The most important causes of death are secondary to pulmonary disorders, heart and renal failure. While the pathogenesis of SSc is not clear, it has important mortality predictors including; onset over 60 year old, anemia, high erythrocyte sedimentation rate, diffuse involvement, presence of Anti Scl-70 and cardiac involvement (6).

Cardiac involvement which is an important mortality predictor may involve myocardium, conduction system, vascular wall, pericardium, pulmonary vessels causing pulmonary hypertension (7). Although up to 70% of patients were reported to have myocardial involvement in pathology specimens, clinical presentation is not present in all cases, called "latent" involvement and in current studies the early diagnosis of latent involvement being an important mortality predictor is emphasized (8, 9).

Myocardial involvement and coronary artery disease

Myocardial disease in systemic sclerosis could be multifactorial: related to associated pulmonary or renal involvement or to hypertension. However, myocardial fibrosis (involving both ventricles despite patent epicardial coronary arteries) has been reported in 70% of patients with SSc in pathology series (9). Focal areas of contraction band necrosis, a reperfusion injury lesion, and myocardial fibrosis have been reported in nearly half of the patients in a study (9, 10). Not all the pathological findings manifest as clinical symptoms and the severity of these pathological findings were unrelated to the concomitant pulmonary and systemic hypertension. However, Raynaud's phenomenon and renal disease were linked to the presence of conduction abnormalities, congestive heart failure, ventricular arrhythmias, and cardiovascular death (7). Diagnosis of cardiac involvement, even if not symptomatic, is an important pathological finding affecting the prognosis of patients. Myocardial disease (including segmental wall motion abnormalities) and impaired coronary flow reserve were reported in the absence of epicardial coronary artery disease (11, 12). Given the absence of small or large-vessel disease, the authors suggested that intermittent obstruction due to vasospasm of the intramyocardial arteries can be responsible for the myocardial abnormalities (11, 12). Besides, a recent angiographic study of 172 systemic sclerosis patients with suspected epicardial coronary disease (based on the presence of exertion dyspnea or angina) rates of coronary artery disease were not different to those with similar gender, age and symptoms (13). Further support for the existence of microvascular disease, particularly spasm has been found in the demonstration of improvement in myocardial perfusion with nifedipine therapy (12, 14) and the detection of segmental wall motion abnormalities and cold-induced perfusion defects in SSc patients with Raynaud's phenomenon (15). Either symptomatic or not, the presence of myocardial and coronary involvement has been found in a number of studies and new diagnostic methods are being applied in the studies in the field of cardiology.

Conduction disease and sudden cardiac death

SSc may affect virtually all cardiac structures and is associated with an increased risk of death (7). Although dyspnea is the most common manifestation of cardiac involvement in SSc, sudden cardiac death, palpitations and syncope may occur (10, 16, 17). In one autopsy study, 6 (13%) of 47 patients experienced sudden death (10). Diffuse conduction abnormalities detected by ambulatory electrocardiography (18-20) have been described in patients with SSc. Furthermore, electrocardiographic abnormalities indicating right ventricular hypertrophy (21, 22), P-wave notching (16), low QRS voltage and nonspecific ST-T wave changes could be seen (16, 23). Supraventricular arrhythmias are common, occurring in approximately two thirds of SSc patients and are more frequent than ventricular tachyarrhythmias (19, 24).

A number of non-invasive studies have been carried out to evaluate conduction system involvement and its relation to mortality. In a study, the signal averaged electrocardiography study revealed that frequent late potentials were present in patients with SSc (25, 26). Greater QT dispersion was detected in another study (27). Ventricular tachyarrhythmias and ectopy found on ambulatory monitoring are linked with increased mortality (24). Ventricular ectopy was common, occurring in 67% of patients. Ectopy defined as more than 100 premature ventricular contractions (PVCs) in 24 hours Holter monitoring was associated with a 4-fold increase in the risk of death, and more than 1000 PVCs was associated with a 6-fold increased risk of death (28). Thus, ambulatory electrocardiography is helpful for the risk stratification of patients with SSc. Generally, CREST syndrome appears to be innocent for arrhythmias (25). Electrophysiological testing has revealed that atrial tachyarrhythmias were more common and sinus node recovery time was greater in patients with SSc. (29) Infra-Hissian conduction was found to be slightly prolonged in patients with SSc and atrioventricular conduction was similar (28). Conduction abnormalities and arrhythmias are related to fibrosis, as opposed to microvascular disease, likely varies with underlying myocardial, anatomic and functional vascular disease.

Pericardial disease

Pericardial disease unlinked to renal failure and characterized by chronic inflammatory changes has been described in histological studies of patients with SSc (11, 30). Pericardial disease is important but appears to be very rare. Two large

studies reported pericardial effusions in 14% of 77 patients (31) and none of 106 patients in echocardiographic evaluation (32).

Right ventricle and pulmonary hypertension

Pulmonary arterial hypertension (PAH) has a very poor prognosis. PAH defined as mean pulmonary arterial pressure greater than 25 mmHg, with pulmonary capillary wedge pressure equal to or less than 15 mm Hg and pulmonary vascular resistance greater than 3 wood units, is a cause of significant morbidity and mortality (33, 34). The prevalence of PAH in patients with SSc depend on the definition of pulmonary hypertension and the method of obtaining the measurements (cardiac catheterization or echocardiography). Using echocardiography, prevalence of pulmonary hypertension in SSc ranges between 35-49% (35-39). But, more recent studies have shown that the prevalence of PAH is indeed between 8 and 12% by cardiac catheterization for diagnosis (40, 41). In all patients with SSc, PAH significantly worsens survival (42). The prevalence of SSc related PAH may be as high as 24 individuals per million, which indicates that SSc related PAH can be more common than other forms of pulmonary artery hypertension. 1-year survival rates for SSc-PAH patients ranging between 50 to 87% (39, 42). Risk factors for the occurrence of PAH in SSc patients including; late-onset disease (37), reduction of diffusing capacity for carbon monoxide (DLCO), Forced vital capacity (FVC)/DLCO ratio of less than 1.6 (43, 44), elevation of serum N-terminal pro-brain natriuretic peptide (N-Tpro-BNP) levels and antibodies (anti-U3 RNP) (45).

Despite the prostaglandins, endothelin receptor antagonists, phosphodiesterase inhibitors and tyrozine kinase inhibitors; its prognosis is worse than PAH associated with other conditions. It may be attributed to the multi-organ involvement of the disease. As early diagnosis and treatment of PAH in patients with SSc improves prognosis, clinicians must keep in mind PAH in patients with dyspnea. Anti-inflammatory and/or antiproliferative therapy along with routine anti-PAH regimen is another therapeutic option in patients with SSc as fibrosis is an important component.

Latent cardiac involvement

Although up to 70% of patients have cardiac involvement, all of the patients do not show clinical manifestations. As the cardiac involvement is an important predictor of mortality, diagnosis of latent cardiac involvement is necessary (9). And some studies were performed with invasive procedures like endomyocardial biopsy for this reason but noninvasive diagnosis of this situation must be the mainstay approach. Cardiac involvement and myocardial fibrosis can be demonstrated by delayed enhanced magnetic resonance imaging (MRI) and 123I-MIBG scintigraphy in patients with SSc (46, 47). However, both scintigraphy and cardiac MRI are not superior to the pathological studies in the detection of myocardial fibrosis. Hirono and coworkers (48) recently reported that TDI echocardiography is more sensitive than conventional echocardiography in the detection of latent and subtle diastolic dysfunction when the systolic functions are normal. This study underscores the possible utility of this technique in the prediction of clinical end-points, such as sudden cardiac death. In addition, tissue Doppler studies with strain rate method revealed the early impairment of contraction and relaxation in SSc patients with normal echocardiographic and radionuclide studies (49). In another study, Mele et al. (50) reported that TDI-derived strain, strain rate, E/Ea can detect impairment of left ventricular functions better than TDI systolic velocities in asymptomatic patients with SSc and normal systolic function. This study verified the early myocardial involvement in these patients. Evaluation of the electromechanical properties of heart in the assessment of latent cardiac involvement is a novel approach. In a recent study from our group, it was demonstrated that there was a heterogeneous prolongation of the duration from the initiation of electrical activity to the mechanical contraction in all segments of the left ventricle. Left ventricular segments were involved heterogeneously with variable severity secondary to the heterogeneous nature of intra-myocardial fibrosis in patients with SSc (8, 51). Left ventricular segmental systolic function abnormality and intraventricular systolic dyssynchrony were thought to be the results of this association.

Normally, all the myocardial segments begin to contract at the same time. The impulse reaches left ventricle via Purkinje's system causing simultaneous contraction that yields an effective ejection. LV dyssynchrony that occurs with myocardial injury, especially in heart failure, impairs global ejection. Various methods from M-mode to speckle tracking are used to evaluate dyssynchrony (52, 53). Parameters of dyssynchrony developed for the evaluation of response to CRT are being studied for evaluation of all diseases known to have myocardial involvement. Evaluation of dyssynchrony in SSc patients who have a high rate of cardiac involvement (Table 1) seems an important tool in early detection of myocardial involvement.

Conclusion

The most important cardiovascular abnormalities associated with SSc are microvascular perfusion abnormalities of the ventricular myocardium resulting in fibrosis, ischemia, conduction disease and systolic dysfunction. Prognosis in SSc is affected by evidence of cardiac involvement. Detection of subclinical cardiac involvement is necessary in routine evaluation of patients with SSc. A broad perspective of basic investigations including ECG and 24 hour ambulatory Holter monitoring to echocardiographic evaluation and endomyocardial biopsy are performed for this reason. Evaluation of the electromechanical properties of the atrium and ventricles in the assessment of latent cardiac involvement is a helpful modality and might help the clinician in therapy decisions. In light of these

Table 1. Cardiac involvement in patients with systemic sclerosis

	Percentage of involvement	Reference no
Myocardial involvement	70%	9
Conduction disease	50-60%	19, 24
Sudden cardiac death	13%	10
Pulmonary hypertension	12-35%	35-40
Pericardial disease	14%	31
Ventricular arrhythmias	67%	28

studies, non-invasive techniques can be useful for early detection of cardiac involvement and prediction of prognosis, thus enabling timely management with new therapeutic approach and evaluating response to medical therapy. Future research is needed to determine an acceptable method and cut-off value for parameters of dyssynchrony which detected from electromechanical properties of the heart.

Conflict of interest: None declared.

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